REMARKS/ARGUMENTS

In response to the Office Action of October 29, 2003, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

In order to provide the Examiner an opportunity to fully consider all of the issues, a Request for Continuing Examination is filed concurrently herewith.

Claim Status/Support for Amendments

The Examiner has indicated that claim 1 is in allowable form, thus claims 36-43 have been rejoined. Claims 36, 41, 42 and 43 have been amended. Claims 2-35 were cancelled in a previous Response (filed on May 30, 2003). Claims 1 and 36-43 are under examination and remain pending in the instant application. Claims 1 and 41-43 have been deemed allowable.

No new matter has been added by the amendments to the specification made herein.

The Prior Art section has been amended at page 4, beginning at line 19 to correct a typographical error in the international application number. The corresponding international publication number has also been added.

The paragraph at page 20, beginning at line 7, was amended to correct a typographical error (moities) and to delete an extraneous word (educable). Support for this change can be found in an objective of the invention at page 17, lines 15-18.

In the Detailed Description section, the term "cerebrospinal fluid" has been added next to abbreviation "CSF" at page 28, line 17 in order to provide proper support for cerebrospinal fluid as recited in claim 38. "CSF" is a well known abbreviation in the biochemical art for cerebrospinal fluid, see, for example, U.S. Patent 4,855,408 to Kuhn et al, column 1, line 59-60. A typographical error within the same paragraph was also amended; skill replaced skilled.

No new matter has been added by the amendments to the claims made herein.

Claim 36 has been amended to more clearly disclose the use of a combination of preparatory steps in conjunction with mass spectrometry techniques (see page 12, lines 2-6 of the instant specification). These preparatory steps maximize the diversity of biopolymers discerned from the sample (see page 11, lines 10-14 and page 20, lines 7-9 of the instant specification). The preparatory steps involve various chromatography protocols that are described in detailed at pages 20-25 of the instant specification.

Claim 41 has been amended to correspond with the isolated biopolymer marker peptide of claim 1.

Claims 42 and 43 were amended to provide proper antecedent basis for the term "kit" in claim 41.

Rejoining of Claims

Applicants thank the Examiner for rejoining claims 36-43 (which were previously withdrawn from consideration as a result of a restriction requirement) with claim 1, which the Examiner has deemed to be in allowable form (as amended in the Response filed on August 25, 2003). Claims 1 and 36-43 have now been fully examined for patentability under 37 CFR 1.104.

Drawings

The corrected drawings filed on May 30, 2003 have been accepted by the draftsman.

Rejections under 35 USC 112 (first paragraph)

Claims 36-40, as presented on May 30, 2003, stand rejected under 35 USC 112, first paragraph, as containing subject matter which allegedly was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time that the invention was filed, had possession of the claimed invention.

The Examiner asserts that the phrase "effective to maximize"(claim 36, line 6) in connection with the elucidation of discernible peptide fragments is not supported by the specification, drawings or claims as originally filed. Additionally, the Examiner asserts that there does not appear to be

support for the word "and" in line 15 of claim 36.

In the interest of compact and efficient prosecution, Applicants have amended claim 36 to remove the phrase "effective to maximize" and this limitation is not recited in any of the remaining pending claims. Additionally, claim 36 has been amended to change "and" to -- or -- as suggested by the Examiner (support for such a change is found at page 28, lines 1-2 of the instant specification).

The Examiner contends that the word "cerebrospinal" does not have written support within the specification as originally filed.

Applicants respectfully disagree with the Examiner's assertion. The abbreviation "CSF" at page 28, line 17 of the specification as originally filed is well known in the art to denote "cerebrospinal fluid", (see U.S. Patent 4,855,408 to Kuhn et al, column 1, line 59-60, attached herewith) thus, no new matter has been added to the disclosure by defining the abbreviation. In order provide explicit support for claim 38, "cerebrospinal fluid" has been added next the abbreviation CSF at page 28, line 17.

Accordingly, Applicants respectfully submit that all recitations, terms and phrases recited in the pending claims find written support in the disclosure as originally filed and thus, respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

Claims 36-40, as presented on May 30, 2003, stand rejected under 35 USC 112, first paragraph, because the Examiner alleges that while the specification is enabling for a portion of a method for diagnosing myocardial infarction, congestive heart failure or intracerebral hemorrhage, does not reasonably provide enablement for a complete method of such diagnosis. Claim 36 allegedly lacks a purification step and any necessary sample preparation step(s) to get the sample into a form that can be analyzed by mass spectrometry between steps (a) and (b). The Examiner states that a patient sample as cited in claims 37 and 38 seems quite complex regarding peptide content and proteins in general. The Examiner asserts further that it does not appear that one of ordinary skill in the art would be able to perform step (b) merely with a generic statement "effective to maximize elucidation of discernible peptide fragments", without some type of purification of fragments.

Applicants respectfully disagree with the Examiner's position.

The "test of enablement" has been established in the case law. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation (see MPEP 2164.01).

The original step (b) of claim 36 is drawn to conducting mass spectrometric analysis on a patient sample in a manner effective to maximize elucidation of discernible peptide fragments contained therein. Applicants respectfully submit that the original phrase

"manner effective to maximize elucidation of discernible peptide fragments" refers to various chromatographic techniques, i.e. purification. The paragraph at page 20, beginning at line 7, clearly indicates that the preparatory steps that were carried out to maximize the diversity of discernible moieties from the sample were chromatographic steps. Additionally, page 20,line 7 to page 25, line 9 of the instant specification disclose specific chromatographic protocols which were carried out as preparatory steps to sequencing with MS technology.

The Examiner further asserts that a sample from a patient as recited in claims 37 and 38, for example, seems quite complex regarding peptide content as well as proteins in general. The Examiner further asserts that it does not appear that one skilled in the art can perform step (b) reasonably in claim 36 merely with a generic "effective to maximize elucidation of discernible peptide fragments" without some type of purification of such fragments out of a myriad of complex proteins, peptide fragments, and other biomolecules in the samples.

Applicants respectfully disagree with the Examiner's assertions.

As established in the paragraphs above, the original phrase "manner effective to maximize elucidation of discernible peptide fragments" refers to various chromatographic techniques, i.e. purification. Three specific types of column chromatography are exemplified in the instant specification; HiQ Anion Exchange,

SEPHAROSE, and HiS Cation Exchange (see pages 21-24). Each type of column contains a resin which is specific for a certain protein characteristic. Thus, multiple columns are applied for the purification of complex samples containing numerous proteins of diverse characteristics.

Chromatography is a very well known technique that has been routinely practiced for many years in the purification of proteins (see attached abstract of Pedro Cuatrecasas PNAS USA 69(5):1277-1281 1972). Thus, Applicants respectfully submit that one of skill in the art would recognize from step (b) of claim 36 as originally written that the manner referred to is chromatography and would further recognize that a plurality of chromatographic techniques may be necessary to maximize the number of components effectively purified from complex mixtures.

However, although Applicants believe that claim 36 as originally written is fully supported by the instant specification as originally filed, in the interest of compact, efficient prosecution, claim 36 has been amended herein to clearly recite a step drawn to preparing a patient's sample to maximize the diversity of biopolymers discernible from the sample prior to evaluating the sample by mass spectrometry.

Accordingly, Applicants assert that the specification, as originally filed, provides sufficient teachings on how to carry out the purification step of the claimed method and further that one of skill in the art would be able to carry out the method of the

instant invention using the information in the disclosure combined with information regarding the purification of protein mixtures known in the art. Thus, the instant invention, as originally filed, satisfies the test of enablement.

In conclusion, Applicants respectfully submit that the specification, as originally filed, fully enables a method reciting a purification step for preparing a patient's sample to maximize the diversity of biopolymers discernible from the sample. Thus, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

Rejection under 35 USC 112 (second paragraph)

Claims 36-40, as presented on May 30, 2003, stand rejected under 35 USC 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

The Examiner asserts that claims 36-40 are incomplete for omitting essential steps, such an omission amounting to a gap between steps. The Examiner alleges claim 36 omits any purification or other necessary sample preparations steps between step (a) and (b) of claim 36 which are required to provide a sample in a form that can be analyzed by mass spectrometry in step (b). The Examiner contends that since the sample seems quite complex with respect to peptide and protein content, it is unclear how one can perform step (b) based upon the limitation "effective to maximize elucidation of

discernible peptide fragments" absent some type of additional purification of such fragment prior to analysis.

Applicants respectfully disagree with the Examiner's assertions.

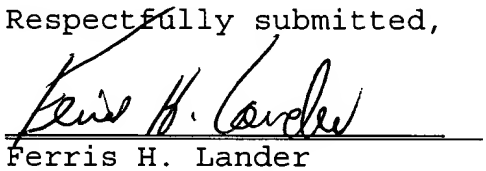
It was established above in the section responding to the "scope of enablement" rejection that the manner recited in the phrase "in a manner effective to maximize elucidation of discernible peptide fragments" is chromatography. Chromatography is a well known process applied to a sample to provide purification prior to analysis of the sample by mass spectrometry. It was also established that the preparing recited in claim 36 as amended herein "preparing said sample to maximize the diversity of biopolymers discernible from the sample" is a protein purification step encompassing chromatography techniques.

Thus, Applicants respectfully submit that claims 36-40 are complete as amended herein and do not omit any essential steps and therefore, Applicants respectfully request that this rejection under 35 USC 112, second paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,



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Proc Natl Acad Sci U S A. 1972 May; 69(5): 1277–1281.

Affinity Chromatography and Purification of the Insulin Receptor of Liver Cell Membranes

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Abstract

Relatively simple and rapid procedures are described for the large-scale preparation of liver membranes that contain virtually all of the high affinity insulin-binding activity of liver homogenates. The presumed insulin recepotr, which is extracted from these membranes in soluble form with Triton X-100, can be further purified by ammonium sulfate fractionation (3-fold purification) or by diethylaminoethyl-cellulose chromatography (60-fold purification). Several insulin-agarose derivatives have been synthesized that can efficiently extract the insulin-binding protein from the detergent extracts of the membranes. The receptor macro-molecule can be eluted from the affinity columns in high (50-80%) yield by use of urea-containing buffers of moderately low pH. The receptor, thus purified by small-scale affinity chromatography experiments, approaches theoretical purity on the basis of its specific activity. This protein is purified about 250,000-fold from the liver homogenate by detergent extraction and affinity chromatography.

insulin-agarose | detergent extraction

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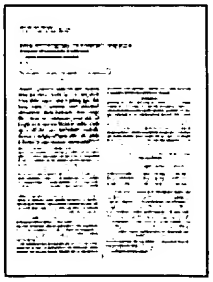
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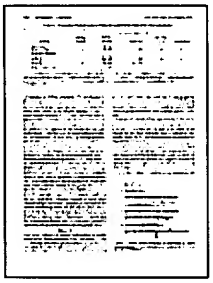
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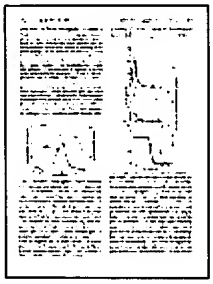
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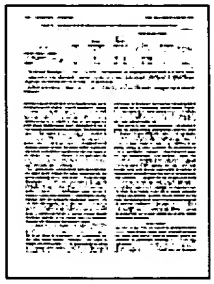
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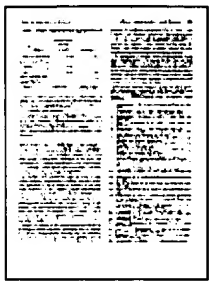

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